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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUGHES, ALICIA R	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
10/12/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@mwzb.com

Office Action Summary	Application No.	Applicant(s)	
	10/796,174	SIEMEISTER ET AL.	
	Examiner	Art Unit	
	ALICIA R. HUGHES	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,and 4-24* is/are pending in the application.

4a) Of the above claim(s) *22 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-21 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims and Examination

Claims 1-2, 4-21, and 24 are pending and the subject of this Office Action. Claims 22-23 are withdrawn from consideration, being drawn to a non-elected invention. See 37 C.F.R. 1.142 (b). Pursuant to the petition decision of 21 October 2009, the Office Action of 17 March 2009 is hereby VACATED.

Applicants' arguments, filed on 10 December 2008, have been fully considered and are deemed to be persuasive regarding the previous rejection. Rejections and objections not reiterated from previous Office Actions are hereby withdrawn.

Upon reconsideration of the pending claims, as presented, the following new rejections are applied. They constitute the complete set of rejections being applied to the instant application presently.

Restriction Requirement and Request for Rejoinder

The Applicants have renewed their request that insofar as the Office has agreed to search the full scope of the genus claims, claims 14-18 should be examined at this time, also, because to do so would pose no serious burden to the Examiner. This request is hereby granted. However, the Applicants are also requesting rejoinder of the process claims at this time.

The Applicants properly note that where product claims are found allowable, process claims that depend from or otherwise require all the limitations of the patentable product may be rejoined. The Office need not consider this request at present, as not claims have been held allowable at this time.

Claim Rejection – 35 U.S.C. §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 4-21, and 24 are rejected under 35 U.S.C. §103(a) as being obvious over Thorpe et al (U.S. Patent No. 6,703,020).[1]

The rejections germane to this portion of the present Office Action as set forth in the Office Actions filed on 02 November 2006, 20 September 2007, and 10 June 2008 are incorporated herein by reference and extended to claims 8, 12-21 and 24.

Thorpe et al teach antibodies that have the ability to maintain VEGF binding to VEGFR1 (Col. 5, lines 29-31). Thorpe et al also teach "the intention of using antibodies that do not

[1] Cited on previous PTO-892.

substantially inhibit VEGF binding to VEGFR1 is to maintain biological functions mediated by VEGFR1" (Col. 5, lines 24-26). The reference further teaches that these antibodies "exhibit a reproducible ability to maintain VEGF binding to VEGFR1 at levels of at least about 88%, about 90%, about 92%, about 95%, or of about 98-99% at any amount between about 100 fold molar excess of antibody over VEGF" (Col. 5, lines 31-35). The variation in the binding levels typifies a modulation in biological function.

In addition, Thorpe et al teach an antibody targeted to the endothelium via a VEGF/VEGF receptor system. More specifically, Thorpe et al teach "a VEGR2-blocking, anti-VEGF antibody may be identified by testing for the ability to inhibit VEGF-mediated endothelial cell growth (inhibiting the mitogenic activity of VEGF)" (Col. 6, lines 48-51). The reference further teaches that "[a]n antibody with an ability to inhibit VEGF-mediated endothelial cell growth will generally exhibit a consistently observed inhibition of VEGF-mediated endothelial cell growth of about 25%, 30%, 35%, 40%, 45%, or 50% or so" (Col. 6, lines 60-63), and that angiopoietin-2 is a ligand for the Tie2 receptor that counteracts blood vessel maturation and stability mediated by angiopoietin-1, thereby acting to disturb capillary structure (Col. 81, lines 38-41). More specifically, Thorpe et al teach that angiopoietin-2 "imparts a negative signal to the target cells and destabilization induced by angiopoietin-2 leads to vessel regression" (Col. 81, lines 42-44). Thorpe et al further teach that "an extreme biasing in the system in favor of regression, by perpetual angiopoietin-2 signaling, may well obliterate the effects of both angiopoietin-1 and VEGF" (Col. 81, lines 54-57).

Thorpe et al teach that angiopoietin-1 is a receptor activator that acts through the Tie2 receptor, to promote the stabilization and the maintenance of mature vessels and it is thought to

"convert immature vessels to []mature vessels by promoting interactions between endothelial cells and the surrounding support cells" (Col 80, lines 40-45). Thorpe et al also teach that angiopoietin-1 has a direct role "… on human endothelial cell and its interaction with other angiogenic molecules … [work to] stabilize vascular structures by promoting the survival of differentiated endothelial cells" (Col. 80, lines 52-56).

Thorpe et al II teach antibodies that specifically inhibit VEGF binding to only one of the two VEGF receptors (Col. 1, lines 18-21), and that these antibodies may be used as part of a combination therapy (Col. 112, lines 14-15). More specifically, Thorpe et al II teach antibodies that "are used simultaneously with, before, or after surgery or radiation treatment; or are administered to patients with, before, or after conventional chemotherapeutic, radiotherapeutic or anti-angiogenic agents, or targeted immunotoxins or coaguligands" (Col. 112, lines 27-34).

Claim 10 of the instant application is drawn to a pharmaceutical composition according to claims 1-8 which comprise as compound I at least … "(d) compounds which inhibit or activate expression of a ligand or of a receptor of the VEGF or Tie receptor system." Thorpe et al II teach "that using a tumor-binding ligand to deliver angiopoietin-1 to tumor blood vessels would readily deliver on the order of 500,000 angiopoietin-1 molecules to a vessel lumen. This would overwhelm the Tie2 receptor system, totally saturating the Tie2 receptors with the angiopoietin-1 ligand" (Col. 80-81, lines 66-67 and 1-4, respectively). As a result of the Tie2 receptors being overly saturated, Angiopoietin-2 would be unable to bind and the combined result would be the inhibition of VEGF. (Thorpe et al II, Col 81, lines 4-6).

Further, Thorpe et al II teach components that induce necrosis in tumors in "combination with non-toxic substances or 'prodrugs.' The enzymes set free by necrotic processes cleave the

non-toxic 'prodrug' into the toxic 'drug', which leads to tumor cell death" (Col. 113, lines 14-20).

Despite all of these teachings, Applicants still claim that their specification teaches that the modulation of two receptor systems unexpectedly results in superior pharmacological effects and that insofar as Thorpe et al is silent with respect to the combination recited in Applicants' claim 1 - which has been amended now to include the limitation "wherein said compound I and said compound II are not identical to one another" - the instant invention is unobvious.

These arguments have been thoroughly considered. With regard to the amended language, the claims still read on the prior art of record, because Thorpe et al disclose treatment by the administration of certain compounds and mixtures thereof, with the operative word being mixtures (Col. 1, lines 16-26 and Col. 3, lines 34-42). It necessarily follows that mixtures or combinations thereof means heterogeneity rather than homogeneity. Thus, the compounds are not necessarily the same. With regard to the Applicants' other arguments, for the reasons previously made of record, they are not deemed to be persuasive. The examples cited by Applicants do not support a synergistic effect inasmuch as Examiner interprets them to be demonstrative of an additive one. In light of the foregoing, the rejection is therefore maintained.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alicia Hughes whose telephone number is 571-272-6026. The examiner can normally be reached from 9:00 AM to 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached at 571-272-0718. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR of Public PAIR. Status information for unpublished applications is available through Public PAIR only. For information about the PAIR system, see http://pair-direct-uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alicia R. Hughes/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614